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Diffusion tensor imaging in studying white matter complexity: A gap junction hypothesis

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Abstract

The role of the prefrontal cortex as an executive oversight of posterior brain regions raises the question of the extent to which the anterior regions of the brain interconnect with the posterior regions. The aim of this study is to test the complexity of rostral white matter tracts, which connect anterior and posterior brain regions, in comparison to caudal white matter tracts and the corpus callosum. Diffusion tensor imaging (DTI) is a modality that measures fractional anisotropy (FA). Higher white matter complexity could result in a decrease of FA, possibly through denser intersection of fiber tracts. DTI was used to determine regional FA in 9 healthy bonnet macaques (*Macaca radiata*). Four regions of interest were included: anterior and posterior limbs of the internal capsule, the occipital lobe white matter, and the corpus callosum. FA of the anterior limbs of the internal capsule was lowest compared to all other regions of interest (Newman-Keuls (N-K); $p < 0.0001$), whereas FA of the corpus callosum was highest (N-K; $p < 0.0001$). The posterior limbs of the internal capsule and the occipital white matter were not distinguishable but exhibited intermediate FA in comparison to the former (N-K; $p < 0.0001$) and the latter (N-K; $p < 0.0001$). The current study demonstrates that FA, a measure of white matter complexity, can vary markedly as a function of region of interest. Moreover, validation of these findings using neurohistological studies and replication in human samples appears warranted.

Keywords

Diffusion tensor imaging; fractional anisotropy; white matter; gap junctions; nonhuman primates; neuroimaging; neurodevelopment

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Introduction

Absolute brain size has been found to be a strong determinant of cognitive abilities across primate species [6]. Moreover, within the brain, prefrontal white matter volume was reported to be disproportionately larger in humans than in other primates [18], suggesting that prefrontal white matter volume and complexity play a key role in brain evolution [18]. Alternatively, the known role of the prefrontal cortex, as a brain region that maintains executive oversight of posterior brain regions, raises the question of the extent to which the anterior regions of the brain interconnect with the posterior regions [1,5,20]. In this study we examined white matter complexity using diffusion tensor imaging (DTI) in order to provide data relevant to this issue.

DTI is a modality that measures fractional anisotropy (FA) – the degree to which water diffuses along the plane of the axons [3]. DTI has been used to assess normal brain functions as well as neuronal abnormalities [16], and the growth of its applications has been exponential over the last decade [26]. Decreased anisotropy can be a biomarker of neuronal pathology; however the correlation between neuronal microstructure and anisotropy is complex and multifactorial [16].

Given that the prefrontal cortex exerts control over other brain regions, particularly the posterior regions, then the rostral white matter tracts (e.g. anterior limb of internal capsule) that connect the prefrontal cortex to the posterior regions (e.g. dorsomedial and anterior thalamic nuclei) should be more complex than the caudal white matter tracts and the corpus callosum that do not connect prefrontal cortex with posterior brain regions. Additionally, disruption of the integrity of white matter tracts disturbs the planar water diffusion, decreasing the FA [3]. Furthermore, a higher level of fiber tracts intersection results in a decrease of FA [26]. Thus, should the prefrontal white matter possess higher complexity compared to that of the rest of the white matter, possibly through denser intersection of fiber tracts, we would predict that healthy rostral white matter tracts linking frontal regions to the rest of the brain would in fact have lower FA in comparison to the caudal white matter tracts or to the corpus callosum. This hypothesis was to be tested in nonhuman primates.

Materials and Methods

Subjects

Subjects were socially-housed in the SUNY-Downstate Nonhuman Primate Facility. The study was approved by the Institutional Animal Care and Use Committees of SUNY-Downstate, Mount Sinai School of Medicine (MSSM), and Yale University School of Medicine. The subjects were healthy male bonnet macaques (*Macaca radiata*) (n = 9) who had been fed ad libitum throughout their life span. Subjects were housed singly or in groups of up to nine animals at the time of neuroimaging. The mean age in lunar months of the subjects was 61.88 ± 30.84 . On the day of the brain scan, study subjects were ushered into familiar carrying cages and transported to Mount Sinai Medical Center imaging facility in a dedicated animal transport van, with climate control. Following the imaging procedures, subjects returned on the same day to their home cages.

DTI Methods

As described in detail in a previous report [12], upon arrival at the scanner, animals were transported to a restraint cage and following a brief restraint period, were given anesthetic agent intramuscularly. Saffan, previously known as CT1341, is an injectable steroid anesthetic for use in cats and monkeys, and as it minimizes motion artifact (relative to ketamine), it was used to conduct the scans. Saffan, administered at a dose of 16 mg/kg, has two bioactive constituents: 12 mg/kg of alphaxalone and 4 mg/kg alphadolone acetate. Infrequently, animals necessitated

subsequent doses of Saffan (25% of initial dose) if there was evidence of motion during the scan because of diminished level of anesthesia. Subjects usually awakened within 20 minutes following completion of the one hour scan. Once anesthesia was achieved, the monkey's head was positioned in a Styrofoam headrest inside a human knee coil, and the forehead was taped to the scanner, to further minimize movement artifact. Subjects were continuously monitored by pulse oximeter during anesthesia. Saffan was not associated with toxic effects or cardiorespiratory depression for any subjects. No other complications from the anesthesia or scan procedure occurred.

DTI data were acquired on a 3 T MRI Siemens Scanner. The protocol for the structural scans consisted of a three-plane sagittal localizer from which all other structural scans were prescribed. The following structural scans were acquired: Axial 3D-MPRage (TR = 2500 ms, TE = 4.4 ms, FOV = 21 cm, matrix size = 256×256, 208 slices with thickness = 0.82 mm); Turbo spin echo T2-weighted Axial (TR = 5380 ms, TE = 99 ms, FOV = 18.3×21 cm, matrix = 512×448, Turbo factor = 11, 28 slices, thickness = 3 mm, skip 1 mm); DTI using a pulsed-gradient spin-echo sequence with EPI-acquisition (TR = 4100 ms, TE = 80 ms, FOV = 21 cm, matrix = 128×128, 24 slices, thickness = 3 mm, skip 1 mm, b-factor = 1250 s/mm², 12 gradient directions, 5 averages). The averaging of the raw DTI data was performed on the eddy current corrected magnitude images during data acquisition. Raw DTI data were transferred to an off-line workstation for post-processing. In-house software written in Matlab v6.5 (The Mathworks Inc. Natick, MA) was used to compute the anisotropy and vector maps. The FA images were then converted to analyze format. In-house developed software on the Matlab platform was used to access regions of interest (ROI) values of the FA images. Primary ROIs included the anterior limbs of the internal capsule, the posterior limbs of the internal capsule, the occipital lobe white matter, and the anterior and posterior corpus callosum (Figure 1).

Data Analysis

Because no laterality or other effects were observed for FA, sides and anterior and posterior corpus callosum were collapsed into a single mean. Since only healthy primates were examined, no between factors were available for a repeated measures analysis. Rather, each region was viewed as contributing independent measures and assigned to one of four groups, anterior limb of the internal capsule (ALIC), posterior limb of the internal capsule (PLIC), occipital white matter (Occ WM) and corpus callosum (CC). An ANCOVA then compared the four regions of interest using age and weight as covariates. Post-hoc Newman-Keuls testing included comparison of ALIC to the other three regions of interest. Parametric testing was confirmed using a non-parametric Friedman's ANOVA for multiple dependent variables.

Results

There was a marked difference of fractional anisotropy between white matter regions of interest in nonhuman primates (Figure 2). Fractional anisotropy of the anterior limbs of the internal capsule was lowest compared to all other regions of interest (Newman-Keuls $p < 0.0001$), whereas fractional anisotropy of the corpus callosum was the highest (Newman-Keuls; $p < 0.0001$). The posterior limbs of the internal capsule and the occipital white matter were not distinguishable but exhibited intermediate fractional anisotropy in comparison to the anterior limbs of the internal capsule (Newman-Keuls; $p < 0.0001$) and the corpus callosum (Newman-Keuls; $p < 0.0001$). Parametric comparison for independent variables were validated using non-parametric analyses for dependent variables [Friedman ANOVA χ^2 (N = 9, df = 3) = 22.73 $p = 0.00005$].

Discussion

The current study supported the hypothesis that healthy anterior white matter tracts, linking frontal regions to the rest of the brain, have lower FA in comparison to caudal white matter tracts or the corpus callosum. To our knowledge, no other studies have directly compared the fractional anisotropy of the anterior white matter to that of the rest of the white matter. However, it has been reported that the corpus callosum has high diffusion anisotropy [5]. Moreover, inspection of published data of human DTI studies suggests higher fractional anisotropy in the corpus callosum compared to other white matter regions such as the internal capsule [2], or the frontal and temporal white matter [15].

It is of great interest to study the complexity of the ALIC as it has been reported to be involved in multiple psychiatric disorders, particularly schizophrenia [14,21,22,28,29] and obsessive compulsive disorder [4,7]. Moreover, the ALIC is involved in two important limbic circuits: the medial limbic circuit (consisted of the hippocampal formation, mammillary bodies, anterior thalamic nuclei, and cingulate gyrus) and the basolateral limbic circuit (connecting the orbitofrontal cortex, dorsomedial thalamic nucleus, amygdala, and anterior temporal cortex) [28]. Furthermore, the ALIC has been increasingly examined as a potential target for deep brain stimulation (DBS) in patients with treatment resistant depression [8] and treatment resistant obsessive compulsive disorder [23]. In addition, using DTI tractography techniques, Gutman and colleagues showed that the ALIC demonstrates widespread projections to the frontal pole, the medial temporal lobe, the cerebellum, the nucleus accumbens, the thalamus, the hypothalamus, and the brainstem [8]. Therefore, the ALIC seems to be part of multiple neural circuits and is subsequently essential to a diversity of normal and pathological brain functions.

In this nonhuman primate study, we demonstrate that FA, a possible measure of white matter complexity, can vary markedly as a function of region of interest. FA is an index ranging from zero to one, with one signifying maximal anisotropy (water diffusion occurring along only one axis). Alternatively, a value of zero means isotropy (water diffusion that is unrestricted and the same in all directions). Though decreased anisotropy can be a biomarker of neuronal pathology, the correlation between neuronal microstructure and anisotropy is multifactorial (for review, see [3] & [16]). Since our sample is composed of healthy subjects, it is unlikely that neuronal pathology contributed to the observed FA difference.

Recall that a voxel size is on the scale of millimeters, whereas a single axon is on the order of micrometers. At present, conventional DTI is incapable of resolving multiple fiber orientations within an individual voxel [25], therefore, we surmise that a higher level of intersections of fiber tracts in the anterior regions of the brain likely accounts for the decrease in the level of anisotropy in these regions. Although a limitation of our DTI protocol might be the 1mm gap between imaging planes. The effects of this would be mainly on smaller tracts or sharp angles; our analysis approach has focused on larger tracts with ROIs well contained inside the tract.

Studies showed flexible changes in the level of anisotropy in multiple brain regions after treatment with different modalities [15,19,27]. Nobuhara and colleagues noticed an increase in the frontal FA after treatment with electroconvulsive therapy of depressed geriatric patients [15]. Yoo and colleagues observed a decrease in the corpus callosum and the internal capsule FA after treatment with citalopram of patients with obsessive-compulsive disorder [27]. Scholz and colleagues reported increase in fractional anisotropy in the subcortical white matter around the intraparietal sulcus of healthy adults following visuomotor skill training [19]. These significant white matter changes, as illustrated by differences in FA, occurred within an interval of 4 to 12 weeks in human adult participants. The authors suggested that these white matter changes may reflect alterations of axonal caliber, myelination, packing density, or directional

coherence [19,27]. However, other studies confirm that intact membranes are the main determinant of anisotropic water diffusion in the brain's white matter [3]. In addition, it now appears that axons are capable of communicating with each other, without utilizing classical neurotransmitters, through gap junctions [9]. Additionally, computational modeling, electrophysiological, and dye coupling studies provided evidence for axo-axonic gap junctions in pyramidal cells [17,24]. Gap junctions are membrane proteins that allow for direct electrical and chemical communication between cells. Gap junction channels allow for the transmission of small molecules up to a molecular mass of 1 KDa. Water has a molecular mass of about 18 Da and can be exchanged by passive diffusion through gap junctional conduits [11]. Thus, axo-axonic water diffusion could potentially contribute to FA reduction. It is therefore highly plausible that at least part of the observed low FA in the anterior brain regions, compared to the posterior regions, may be influenced by the abundant presence of gap junctions in these highly connected brain regions. Furthermore, it has been reported that gap junctions have activity-dependent plasticity and may be modulated by local factors (e.g., voltage, pH, and calcium), neurotransmitters (e.g., dopamine), and medications (e.g., carbenoxolone) [10,13]. This raises the possibility that part of the fractional anisotropy changes, noticed in the above mentioned studies, are the result of gap junction coupling modulation and state.

To our knowledge, this is the first study that directly compares the FA among different regions of interest in the brain rather than between same regions of interest in different groups. Examining white matter complexity using DTI in nonhuman primates allows for future neurohistological studies of the same sample, an option not available in human studies. This study provides additional evidence supporting the view that white matter tracts are malleable [19] and may represent an important primate neuroevolutionary component [18]. Moreover, although the precise substrate by which axons communicate with each other remains speculative, the findings of this study introduce the hypothesis of high abundance of gap junctions in the increasingly complex anterior white matter, as evidenced by low FA. However, it remains to be demonstrated, either in humans or in animals, whether individual variations in axo-axonal connectivity influence fractional anisotropy or account for functional attributes and psychopathology.

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Figure 1. Diffusion Tensor Imaging of Nonhuman Primates: Regions of Interest Voxel Placement

DTI data were acquired on a 3 T MRI Siemens Scanner. The protocol for the structural scans consisted of a three-plane sagittal localizer from which all other structural scans were prescribed. Raw DTI data were transferred to an off-line workstation for post-processing. In-house software written in Matlab v6.5 (The Mathworks Inc. Natick, MA) was used to compute the anisotropy and vector maps. The fractional anisotropy (FA) images were then converted to analyze format. In-house developed software on the Matlab platform was used to access regions of interest (ROIs) values of the FA images. Primary ROIs included the anterior limbs of the internal capsule, the posterior limbs of the internal capsule, the occipital lobe white matter, and the anterior and posterior corpus callosum.

Figure 2. Comparison of Fractional Anisotropy in Nonhuman Primates by White Matter Regions of Interest

Fractional Anisotropy (FA) of the anterior limbs of the internal capsule (ALIC) was lowest compared to all other regions of interest (ROIs) (Newman-Keuls (N-K); $p < 0.0001$)***, whereas FA of the corpus callosum (CC) was highest (N-K; $p < 0.0001$). The posterior limbs of the internal capsule (PLIC) and the occipital white matter (OCWM) were not distinguishable but exhibited intermediate FA in comparison to the former (N-K; $p < 0.0001$) and the latter (N-K; $p < 0.0001$).